Finasteride and Prostate Cancer: A Commentary

CHANNING J. PALLER,^a THOMAS J. SMITH^{a,b}

^aDepartment of Oncology and ^bProgram for Palliative Medicine, Johns Hopkins Medical Institutions, Baltimore, Maryland, USA

Disclosures: The authors indicated no financial relationships.

Prostate cancer management has focused on early detection and treatment, but the prolonged development cycle of prostate cancer suggests that prevention may be a preferable approach. Finasteride and dutasteride, inhibitors of 5 α -reductase, inhibit conversion of testosterone to dihydrotestosterone (a potent androgen) and have low toxicity, which makes them attractive chemopreventive agents. Both drugs have been proven successful in treating benign prostatic hyperplasia (BPH) and have been approved by the U.S. Food and Drug Administration (FDA) for this indication [1]. Lower doses of finasteride have also been approved for treatment of male pattern baldness [2]. There was great hope that they would be safe, easy, and effective chemoprevention agents against prostate cancer, but studies show otherwise.

In this issue of *The Oncologist*, Kao and colleagues from Taiwan report on the most recent study that shows finasteride use was associated with an actual increase in risk of prostate cancer [3]. They identified 1,489 patients with cancer and BPH in the Taiwanese National Health Insurance registry and carefully matched three patients without cancer. The use of finasteride was associated with an increased risk of prostate and overall cancer (prostate cancer risk increased with an odds ratio of 1.9; overall cancer odds ratio was 1.5). Use of dutasteride was associated with no reduction in risk of prostate cancer and an increased risk of renal cancer. These disappointing results are in line with several other randomized trials investigating the use of these drugs for chemoprevention.

CLINICAL TRIAL RESULTS

The Prostate Cancer Prevention Trial (PCPT) randomly assigned 18,882 men who had a prostate-specific antigen level at or below 3.0 ng/mL, were age 55 or older, and had a normal digital rectal examination, to finasteride (5 mg/day) or placebo for 7 years [4]. The study reported a decrease of 24.8% in prevalence of biopsy-proven prostate cancer in the finasteride population (803 of 4,368 men; 18.4%) compared with placebo

(1,147 of 4,696 men; 24.4%). Urinary symptoms were less common in the finasteride group. However, there was no documented evidence of increased survival in the finasteride group. In addition, a 27% increased risk of high-grade disease (Gleason score ≥ 7) was seen in the finasteride group (280 of 4,368 men; 6.4%) compared with the placebo group (237 of 4,692 men; 5.1%). Despite the increase in high-grade disease, only five men died of prostate cancer in each group. In all, 97.7% of tumors in the finasteride group and 98.4% of tumors in the placebo group were T1 or T2. Finasteride-treated men were more likely to experience more frequent sexual side effects.

In the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, 6,729 men were randomly assigned to dutasteride or placebo for 4 years [5]. Men in the dutasteride group experienced 22.8% less incidence of biopsy-proven prostate cancer (659 of the 3,305 men in the dutasteride group, as compared with 858 of the 3,424 in the placebo group). No significant difference was found in the frequency of high-grade disease in patients with Gleason scores ≥ 7 . However, there was a trend toward high-grade disease in patients with Gleason scores ≥ 8 in the dutasteride group, with a significant increase in high-grade disease in that group in years 3 and 4 of the study.

Based on these results, the FDA did not approve the use of either finasteride or dutasteride for prostate cancer prevention; the advisory committee vote was unanimous (17 to 0). Of note, African-American men are the highest risk group for prostate cancer, but they were underrepresented in both of these studies (2.3% in the PCPT study and 3.7% in the REDUCE study).

COST EFFECTIVENESS OF FINASTERIDE

The cost of finasteride compared to the benefits has been a concern given the unsustainable increases in cancer care costs in the United States [6–8]. Increasingly, most health care entities are looking to ensure reasonable value for new expenditures [9]. The current U.S. price to the consumer for 5 mg of finas-

Correspondence: Channing Paller, M.D., Assistant Professor of Oncology, Johns Hopkins Medical Institutions, Sidney Kimmel Comprehensive Cancer Center, 401 North Broadway, Room 1363, Baltimore, MD 21231-1146, USA. Telephone: 410-955-8893; Fax: 410-955-8587; e-mail: cpaller1@jhmi.edu Received April 12, 2012; accepted for publication June 5, 2012; first published online in *The Oncologist Express* on June 20, 2012. ©AlphaMed Press 1083-7159/2012/\$20.00/0 <http://dx.doi.org/10.1634/theoncologist.2012-0165>

Table 1. Effectiveness and cost-effectiveness of finasteride as the primary prostate cancer preventative agent

Study	Effectiveness from PCPT	Cost-effectiveness ratio	Comment
Zeliadt et al. [11]	24.8% decrease in PC; 27% increased risk of high-grade PC	\$1,660,000/life yr \$200,000/QALY	Used \$2/pill. Improvement in quality of life attributed to effects on BPH. To be acceptable, cost would have to be reduced by 50%, and finasteride would have to prevent high-grade as well as low-grade disease.
Svatek et al. [12]	24.8% decrease in PC; 27% increased risk of high-grade PC	\$1,107,000/life yr	Finasteride would have to cost \$160 a year to be less than the threshold of \$100,000/life yr.
Svatek et al. [13]	24.8% decrease in PC; 27% increased risk of high-grade PC	\$122,747/QALY	Quality adjustments made for reducing symptoms of benign prostatic hyperplasia.
Reed et al. [14]	24.8% decrease in PC; no increase for high-grade PC	\$89,300/QALY	Incorporates family history and genetic polymorphisms for PC risk. Assumes that finasteride reduces risk of all grades of cancer by 25% and that those at highest risk have the same 25% risk reduction; neither assumption is supported by the current data.

Abbreviations: PCPT, Prostate Cancer Prevention Trial; QALY, quality-adjusted life year.

Table 2. Recommendations for physician communication concerning the use of 5 α -reductase inhibitors

Source	Recommendation
American Society of Clinical Oncology and American Urological Association [17]	"It is recommended that the physician: 1. inform the man who is considering a 5-ARI that these agents reduce the incidence of prostate cancer, and be sure to be clear that these agents do not reduce the risk of prostate cancer to zero; 2. discuss the elevated rate of high-grade cancer observed in the PCPT and inform men of the potential explanations; 3. make it known to men that no information on the long-term effects of 5-ARIs on prostate cancer incidence exists beyond approximately 7 years, and that whether or not a 5-ARI reduces prostate cancer mortality or increases life expectancy remains unknown; 4. inform men of possible but reversible sexual adverse effects; and 5. inform men of the likely improvement in lower urinary tract symptoms."
Up-To-Date [18]	"(a) For men who consider preventing cancer more important than the side effects and uncertainties associated with chemoprevention, we suggest therapy with a 5-AR inhibitor. (b) For those more concerned about the side effects and uncertainties of a 5-AR inhibitor, we suggest not using chemopreventive therapy with a 5-AR inhibitor."
American Cancer Society [19]	"Researchers are still watching the men in the clinical trials of finasteride and dutasteride to see if the drug had an effect on how long the men live. At this time, not all doctors agree taking finasteride or dutasteride specifically to lower prostate cancer risk is a good thing. Men who want to know more about this should discuss it with their doctors."
Health Canada [20]	"Both clinical trials showed that the possible benefits of these drugs in preventing low-grade prostate cancer are small relative to the risk of developing high-grade prostate cancer. Finasteride and dutasteride are not approved for the prevention of prostate cancer in Canada."

Abbreviations: 5-AR, 5 α -reductase; 5-ARI, 5 α -reductase inhibitor; PCPT, Prostate Cancer Prevention Trial.

teride is about \$1 a day (drugstore.com, accessed April 10, 2012). Most studies have shown that the cost-effectiveness ratio of finasteride is many times worse than the U.S. standard, whether one uses the traditional \$50,000 per additional year of life or more appropriate estimates of \$150,000–\$200,000 [10].

As shown in Table 1, the cost-effectiveness ratio of finasteride is well over usual thresholds, and the cost would have to

be reduced to half the current price to meet the threshold of \$100,000 per life year. Reed and colleagues used a 14-single nucleotide polymorphisms and family history prediction model to "target" individuals at highest risk; they derived a value closer to accepted thresholds. However, their model makes several assumptions that are not supported by the current evidence, including the following: (a) there is no increased

risk of high-grade cancers: (b) finasteride is equally effective at preventing all grades of cancer (not just low-grade cancers); and (c) finasteride is equally effective in high-risk populations. In summary, the drug lacks sufficient effectiveness at the current price to meet cost-effectiveness thresholds.

COMMUNICATION BETWEEN PHYSICIANS AND PATIENTS

The clinical trial results created a dilemma for physicians. Rather than establishing finasteride and dutasteride as safe and effective chemoprevention agents, the trial results demonstrated substantial chemoprevention but at the cost of increased risk of high-grade prostate cancer and a small increased risk of sexual adverse effects. In contrast, the breast cancer chemoprevention drugs tamoxifen [15] and raloxifene [16] were effective chemoprevention agents and did not increase the rate of high-risk cancer. There is no other effective strategy for chemoprevention; vitamin E and

selenium are not recommended. None of the available guidelines strongly suggest finasteride or dutasteride use, as shown in Table 2. Additional research is essential to determine if any agent is effective in high-risk populations, such as African American men, individuals with family history, or individuals with genetic risk.

Physicians considering the use of 5 α -reductase inhibitors should counsel their patients in accordance with guidance from the American Society of Clinical Oncology (Table 2). The ideal candidate for finasteride or dutasteride is a patient with BPH with a family history of prostate cancer and/or other reasons to be concerned about developing prostate cancer; the candidate should be willing to accept the risk of developing a high-grade cancer and remain under close surveillance. Patients concerned about the risk of developing high-grade prostate cancers may be prescribed alternative agents to treat BPH, such as α -blockers. Most patients and physicians will await the development of more effective agents with less potential risk.

REFERENCES

1. McConnell JD, Roehrborn CG, Bautista OM et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med* 2003;349:2387–2398.
2. Rossi A, Cantisani C, Scarno M et al. Finasteride, 1 mg daily administration on male androgenetic alopecia in different age groups: 10-year follow-up. *Dermatol Ther* 2011;24:455–461.
3. Liang J-A, Sun L-M, Lin M-C et al. A population-based nested case-control study in Taiwan: Use of 5 α -reductase inhibitors did not decrease prostate cancer risk in patients with benign prostate hyperplasia. *The Oncologist* 2012;17:986–991.
4. Thompson IM, Goodman PJ, Tangen CM et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med* 2003;349:215–224.
5. Andriole GL, Bostwick DG, Brawley OW et al. Effect of dutasteride on the risk of prostate cancer. *N Engl J Med* 2010;362:1192–1202.
6. Mariotto AB, Robin Yabroff K, Shao Y et al. Projections of the cost of cancer care in the United States: 2010–2020. *J Natl Cancer Inst* 2011;103:117–128.
7. Bach PB. Limits on Medicare's ability to control rising spending on cancer drugs. *N Engl J Med* 2009;360:626–633.
8. Aaron HJ, Ginsburg PB. Is health spending excessive? If so, what can we do about it? *Health Aff (Millwood)* 2009;28:1260–1275.
9. Smith TJ, Hillner BE. Bending the cost curve in cancer care. *N Engl J Med* 2011;364:2060–2065.
10. Hillner BE, Smith TJ. Efficacy does not necessarily translate to cost effectiveness: A case study in the challenges associated with 21st-century cancer drug pricing. *J Clin Oncol* 2009;27:2111–2113.
11. Zeliadt SB, Etzioni RD, Penson DF et al. Lifetime implications and cost-effectiveness of using finasteride to prevent prostate cancer. *Am J Med* 2005;118:850–857.
12. Svatek RS, Lee JJ, Roehrborn CG et al. The cost of prostate cancer chemoprevention: A decision analysis model. *Cancer Epidemiol Biomarkers Prev* 2006;15:1485–1489.
13. Svatek RS, Lee JJ, Roehrborn CG et al. Cost-effectiveness of prostate cancer chemoprevention: A quality of life-years analysis. *Cancer* 2008;112:1058–1065.
14. Reed SD, Scales CD Jr., Stewart SB et al. Effects of family history and genetic polymorphism on the cost-effectiveness of chemoprevention with finasteride for prostate cancer. *J Urol* 2011;185:841–847.
15. Fisher B, Costantino JP, Wickerham DL et al. Tamoxifen for the prevention of breast cancer: Current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 2005;97:1652–1662.
16. Vogel VG, Costantino JP, Wickerham DL et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA* 2006;295:2727–2741.
17. Kramer BS, Hagerty KL, Justman S et al. Use of 5-alpha-reductase inhibitors for prostate cancer chemoprevention: American Society of Clinical Oncology/American Urological Association 2008 Clinical Practice Guideline. *J Clin Oncol* 2009;27:1502–1516.
18. Crawford ED. Chemoprevention strategies in prostate cancer. Available at <http://www.uptodate.com/contents/chemoprevention-strategies-in-prostate-cancer>. Accessed June 12, 2012.
19. American Cancer Society. Prostate cancer. Available at <http://www.cancer.org/Cancer/ProstateCancer/DetailedGuide/prostate-cancer-prevention>. Accessed June 12, 2012.
20. Health Canada. Finasteride (Proscar, Propecia) and dutasteride (Avodart, Jalyn) may increase the risk of high-grade prostate cancer. Available at http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2012/2012_38-eng.php. Accessed June 12, 2012.

See the accompanying article on pages 986–991 of this issue.